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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/965,807 | 10/01/2001 | Reuben Matalon | SHUTT-1 C1 | 3645 |

23599 7590 10/07/2005

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| EXAMINER | |
|---|---|
| MAYER, SUZANNE MARIE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1653 | |

DATE MAILED: 10/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/965,807 | MATALON ET AL. | |
| | Examiner | Art Unit | |
| | Suzanne M. Mayer, Ph.D. | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *22,24,67-75,89,90 and 92-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-75,89,90 and 92-94* is/are rejected.

7)☒ Claim(s) *22 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on July 8, 2005 has been entered.

### *Withdrawal of Allowability and Status of the Claims*

2. The previous Notice of Allowability dated April 8, 2005 hereby withdrawn bases upon new claim rejections. Claims 22, 24, 67-75, 89-90 and 92-94 are pending and under examination in this application. All other claims have been cancelled.

### *Claim Objections*

3. Applicant is advised that should claim 70 be found allowable, claim 71 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

### *Claim Rejections - 35 USC § 112 – 2nd paragraph*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Definitions which clearly and distinctly point out what the single letter amino acid representations are for the claimed substitutions is needed. For example, the addition of a clause at the end of the claim citing, whereby E is glutamate, A is alanine, Y is tyrosine and X is any naturally occurring amino acid would over come this rejection.

### *Claim Rejections - 35 USC § 112 – 1st paragraph*

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 68, 93 and 94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to biologically active fragments of an isolated human aspartoacylase of SEQ ID No: 2. However, *Vas-Cath Inc. V. Mahurkar*, 19USPQ2d

1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."* The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."

The multitude of possibilities of biologically active fragments which meet the limitations of the claims are vast. Thus, since claims are drawn to so many different combinations of potential polypeptides, the skilled artisan cannot necessarily envision the detailed structures of each and every different biologically active fragment of human aspartoacylase because it is not described in the specification which amino acids of the 313 of SEQ ID No: 2 are absolutely essential and critical for the peptide to maintain *both* its structure and functionality. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the methods of making the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or making it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

8. Claims 68, 93 and 94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, the quantity of experimentation would be large since there are myriad of peptide fragments which may or may not possess biological activity of human aspartoacylase, ranging from a two amino acid peptide fragment up to one amino acid less than the full length protein. However, there is no requirement in the claims that the there needs to be a minimum fragment length which spans essential

amino acids in order for said peptide to maintain structure and function equivalent or similar to the full length protein. The amount of guidance in the specification is zero with regard to a specific length that the fragments need to be, if any, in order to have the correct structural conformation and activity of the full length recombinant proteins. No working examples are present of fragments. The nature of the invention is such that many fragments of many different lengths may or may not have the proper structure and/or activity. The state of the prior art is that many peptides have been produced which possess no structure or function whatsoever. The relative level of skill in this art is very high. The predictability as to what fragment will have which the proper structure and function is low. The claim reads on fragments from a single di-peptide up to one amino acid less than the full-length protein.

When the factors are considered in their entirety, the Wands analysis dictates a finding of undue experimentation and thus, the claims are not enabled.

9. Claim 92 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human aspartoacylase that has an altered ability to hydrolyze N-acetyl-aspartic acid where the altered ability is derived from amino acid substitutions at positions 285, 231 or 305 of SEQ ID No: 2, does not reasonably provide enablement for all enzymes that are 95% identical to SEQ ID No: 2 that have altered abilities to hydrolyze N-acetyl-aspartic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants have not provided any information regarding which other human mutant aspartoacylases may have a decreased activity. Furthermore, there is no indication where the active site even occurs or where other substitutions might occur or a way in which to even predict which mutations might induce altered abilities to hydrolyze N-acetyl-aspartic acid. Thus, a skilled artisan has merely been provided with an invitation to experiment.

### *Claim Rejections - 35 USC § 102*

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 67, 69-75, 89, 90,92 rejected under 35 U.S.C. 102(b) as being anticipated by Matalon et al. (J. Inher. Dis., 1989, 12, 329-331 – Cited on the IDS of 5-18-2005). Matalon et al. teach that they have isolated and purified human aspartoacylase. Specifically, cells from patients were cultivated in Matalon's modified Eagle's medium (p. 329, last paragraph), and that aspartoacylase was purified to homogeneity from human (and bovine) brain. Furthermore, bases upon SDS-gel electrophoresis, the molecular weight was determined to be 58 kDa (this was reported as unpublished results). The claims stand rejected because by all comparable data, the invention now claimed and the protein of the prior art are the same or equivalent protein because the genus and species of the source is identical, and the relative molecular weight of the

protein isolated and reported is identical to that of the instant SEQ ID No: 2. This, therefore, anticipates the instant claimed invention because the protein will evidence the same or equivalent amino acid sequence whether the amino acid sequence is known or not, as the amino acid sequence is a descriptive characteristic of a protein or polypeptide and is merely an inherent characteristic.

The limitations in the claims which state that the human aspartoacylase SEQ ID No: 2 is produced by recombinant methods carries no patentable weight because whether or not the protein is isolated and/or purified from a recombinant source or from an indigenous source (humans in this instance) does not alter the protein in any way. It is still the exact same protein. (Relevant to claims 74, 75, 89 and 90).

The limitation stated in claim 73, is ultimately still a composition with an intended use limitation which does not change the fact that it is materially and patentably the same human aspartoacylase SEQ ID No: 2 composition.

Finally, there are several different sources of prior art which indicate that human aspartoacylase has been isolated and purified and thus the claimed invention is not novel over such prior art. See References of Interest below.

***References of Interest – Not relied upon***

11. Kaul et al. (a) (American Journal of Human Genetics, 1998, 43, p. A10 – Cited in on the PTO-892 from 7-2-2004) teach that human aspartoacylase has been purified to more than 1100 fold using conventional column chromatography techniques (see lines 10-12).

12. Kaul et al. (b) (J. Neurochem. 1991, 56, 1, 12-135 – Cited on the IDS of 12-18-2001) teach the purification and characterization of aspartoacylase from bovine brain. However, they also state that aspartoacylase from human brain and cultured skin fibroblasts is also a 58 kDa monomer (like the bovine aspartoacylase) and that it follows a similar purification scheme to the bovine aspartoacylase.

13. Kaul et al. (c) (Nat. Genet., 1993, 5, pp. 118-123) teach the cloning of the human aspartcacylase cDNA. However, in the 2nd introductory paragraph on p. 118, it is taught that aspartoacylase has been purified and characterized from bovine brain and from other bovine and human sources, which then references the Kaul et al. (b) article described above.

***Conclusion***

14. Claims 67-75,89,90 and 92-94 are rejected. Claims 22 and 24 are objected.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.30am to 4.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SMN
23 September 2005

ROBERT A. WAX
PRIMARY EXAMINER